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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,879	01/29/2007	Lynette Robyn Griffiths	FISHR24.001APC	2661

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/571,879	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on 3/2/2010 is acknowledged. Claims 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 14-20 have been amended to method claims depending from claims 1 or 9 and have been placed in Group I. Accordingly, an action on the merits of claims 1-20 and 23-25 is set forth below.

2. Applicant is advised that should claim 14 be found allowable, claim 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-20 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention and the breadth of the claims:

The claims (claim 1) are broadly drawn to a method of determining whether any individual has a predisposition to migraine comprising obtaining a biological sample from said individual that comprises at least one nucleic acid that comprises at least a fragment of any female steroid sex hormone receptor gene and determining whether there is any polymorphism in the sequence wherein the presence of the polymorphism indicates that said individual has an increased predisposition to migraine compared to an individual without the polymorphism. The claims are further broadly drawn to such methods which comprise determining whether there is a polymorphism in each of two female steroid sex hormone receptor gene fragments (claim 9). The claims are further limited to ESR1 and/or PGR gene, as well as specific polymorphisms (ESR1 at position 2014 and a 306 base pair insert in PGR). The claims are broadly drawn to detection of any polymorphism be means of amplification, nucleic acid digestion [in some embodiments limited to BTG1], and gel electrophoresis. Claim 13 is limited to migraine with aura or migraine without aura. The term individual broadly encompass any species. The term "polymorphism" is broadly defined by the specification to include any mutation, insertion or deletion (page 8).

The nature of the invention, therefore, requires the knowledge of predictive associations between migraine and any polymorphism or mutation in any female steroid sex hormone receptor gene for any subject.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and the presence and absence of working examples:

The specification teaches 2 different case/control studies which analyzed the association between the ESR1 G2014A SNP (rs2228480) and the PROGINS 306 base pair insertion (rs1042838) in intron 7 of the PGR gene. In the first study of 275 migraineurs and 275 unrelated controls, the specification teaches a statistically significant association between the ESR1 polymorphism and migraine with aura (MA), migraine without aura (MO) in both males in females (page 20). However in the second replication study of 300 migraineurs and 300 unrelated controls, the statistical significance was only found for MA subgroup as well as females. For the PGR PROGINS polymorphism, the specification teaches a statistically significant result for MO subgroup as well as females (page 21) in the first study, but only for the MA subgroup in the second replication study.

The claims are not limited to human patients, and therefore encompass detection in any species, including any mammalian species such as mouse, dog, horse, etc. The nature of the invention requires a predictable correlation between any mutation or polymorphism in any gene which fits within the broad scope encompassed by the claims and any migraine. However, it is not known whether the studied polymorphisms exists in other species, or whether other polymorphisms would be predictably associated with migraine in other species.

The specification provides no predictable association that any alteration, in any female steroid sex hormone receptor gene, indicates a predisposition for migraine. The specification does not teach how the polymorphisms studied, in either gene, affect the function of either gene or how they are associated with migraine in any individual. No common element or attributes of the sequences are disclosed which would permit selection of sequences as functional

polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with migraine is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, and substitutions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any migraine phenotype are described in the specification. Even in the narrower dependent claims, such as claims 2, 4, 7, 10, 15-17, 19, and 21, which are directed to fragments of exon 8 of ESR1 or intron 7 of PGR, the claims encompass any nucleotide variants however only a specific nucleotide change has been taught in the specification for each. The specification does not teach how these polymorphisms are associated with migraine for the skilled artisan to be able to predictably identify polymorphisms or mutations that would have the same effect. The polymorphisms shown are therefore not representative of the genus of any polymorphism associated with migraine because it is not clear which polymorphisms or mutations would have the same affect.

The state of the prior art and the predictability or unpredictability of the art:

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher. The high level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Because the claims encompass any subject organism, it is relevant to point out the unpredictability in extrapolating results regarding the asserted association of an allele with a

phenotype in humans to any other organism. Similar nucleotide sequences may encode polypeptides with markedly different functionalities. Such a possibility is exemplified by Juppner (Juppner; Bone, vol 17; 1995, pp.39S-40S), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

With regard to the specific polymorphisms taught in the specification, it is noted that certain results were not replicated in applicants own follow up study. With regard to the predictability in the art regarding association studies, Lucentini (The Scientist; 2004, vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Similarly, Hegele (Arterioscler. Thromb. Vasc. Biol.; 2002, Vol 22, pages 156-1061) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see

'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

In the instant invention, the level of complexity and unpredictability is also borne out in simply establishing that the polymorphisms studied are associated with migraine. As already noted, applicants own replication study failed to provide statistically significant correlations. Further, a number of studies have been undertaken to confirm the findings taught in the specification with little success. With regard to the ESR1 G2014A (rs2228480) polymorphism: Corominas (Corominas et al; European Journal of Neurology, vol 16, 413-415; 2009), Kaunisto (Kaunisto et al; Cephalagia; vol 26, pages 1462-1472, 2006), and Oterino (Oterino et al; Neuroreport, vol 17, pages 61-64, 2006) teach that no association was found for the ESR1 rs2228480 polymorphism. With regard to the PGR PROGINS polymorphism, Corominas teaches that no association was found between this polymorphism and migraine, while Joshi (Joshi et al; Cephalagia, vol 30, pages 311-320; 2010) teaches a protective effect was found. Conclusions drawn by many of these studies are that genetic variants in either gene are not associated with migraine pathogenesis.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of each position in female steroid sex hormone receptor gene, including the specific polymorphisms studied to determine whether any alteration at each position is associated with migraine. As

neither the prior art nor the specification provide guidance as to which alterations at positions throughout ESR1 or PGR are and are not associated with migraine, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable, as exemplified by the art cited above. Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims, the extensive negative teachings in the art, and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Conclusion

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Mondays from 9:00 AM to 1:00 PM, and Tuesdays & Thursdays from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571) 272-0731. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Jehanne Sitton/
Primary Examiner
Art Unit 1634